

language should read: (including primary, C₁-C₆ alkyl and phenyl secondary and tertiary), amino,

A clean copy of the claims as corrected is attached to this response.

Applicants thank the Examiner for the observations on the claims before commencement of examination on the merits, and request an early consideration of the claims directed to Group 2.

Date: 29 OCT 01

Registration no. 35195

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Respectfully submitted,


SIGNATURE OF PRACTITIONER

J. Mark Hoch

Elan Pharmaceuticals, Inc.

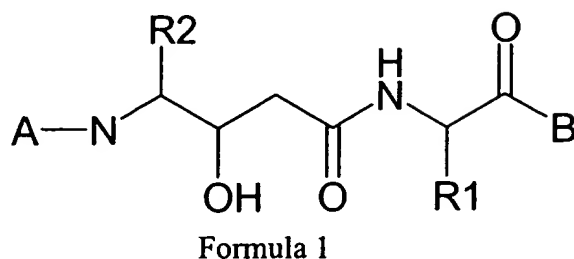
800 Gateway Boulevard

South San Francisco, CA

94080

Clean copy of claims corrected in this response:

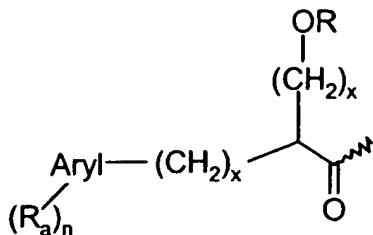
1) A compound of formula 1



wherein:

A is

i)



wherein Aryl is mono or bicyclic and has from 5 to 10 ring atoms and may optionally include up to 3 heteroatoms chosen from N, O and S;

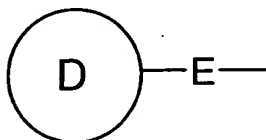
each x is independently 0, 1 or 2;

R is H, C₁-C₆ alkyl, phenyl or benzyl wherein each phenyl ring is optionally substituted with up to two groups independently selected from -OH; -CH₂OH, -CO₂H, -CF₃, Cl, Br, F; and C₁-C₂ alkyl;

each R_a is independently selected from the group consisting of H, OH, C₁-C₃ alkyl; C₁-C₆ alkylacylamino, C₁-C₆ alkylacyloxy, C₁-C₆ alkyloxy, C₁-C₆ alkylthioxy, amido (including primary, C₁-C₆ alkyl and phenyl secondary and tertiary), NH₂, mono and di(C₁-C₆ alkyl and phenyl) amino, carbamyl (including C₁-C₆ alkyl and phenyl amides and esters), carboxyl (including C₁-C₆ alkyl and phenyl esters), carboxy(C₂-C₅)alkyloxy and N-heterocyclacyl;

and n is 1 or 2;

ii)



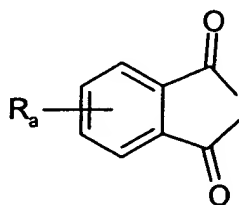
wherein D is chosen from aryl having 5 to 6 atoms, optionally including up to 2 heteroatoms selected from the N, O, and S; fused aryl of 8 to 14 atoms optionally including up to 3 heteroatoms selected from the N, O, and S; mono or fused cycloalkyl having 5 to 12 carbon atoms; and mono or fused heterocycloalkyl having 5 to 12 carbon atoms including up to 3 heteroatoms selected from N, O, and S; biaryl, diaryl ether; diarylketone, and phenyl(C₁-C₈) alkyloxyaryl;

and wherein E is a divalent group chosen from carbonyl, sulfonyl, C₁-C₃ alkylene, -X- (C₁-C₃) alkylcarbonyl wherein X is chosen from N, O and S, or E is merely a bond;

and D may optionally be substituted with up to two groups chosen from OH, C₁-C₃ alkyl; C₁-C₆ alkylacylamino, C₁-C₆ alkylacyloxy, C₁-C₆ alkyloxy, C₁-C₆ alkylthioxy, amido (including primary, C₁-C₆ alkyl and phenyl secondary and tertiary), NH₂, mono and di(C₁-C₆ alkyl and phenyl) amino, carbamyl (including C₁-C₆ alkyl and phenyl amides and esters), carboxyl (including C₁-C₆ alkyl and phenyl esters), carboxy(C₂-C₅)alkyloxy, N-heterocyclacyl, C₁-C₃ alkylsulfonyl, sulfonamide and C₁-C₃ alkylsulfonamide;

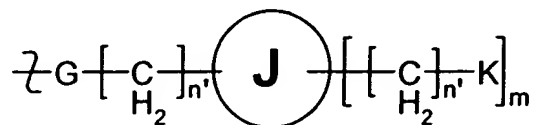
iii) C₁-C₆ alkanoyl; C₂-C₆ alkenoyl; and methylthioC₁-C₃ alkanoyl, any of which may be substituted with up to two groups chosen from OH, C₁-C₆ alkylacylamino, C₁-C₆ alkylacyloxy; C₁-C₆ alkyloxy; C₁-C₆ alkylthioxy, amido (including primary, C₁-C₆ alkyl and phenyl secondary and tertiary), amino, C₁-C₆ alkyl and phenyl amino, carbamyl (including C₁-C₆ alkyl and phenyl amides and esters), carboxyl (including C₁-C₆ alkyl and phenyl esters), carboxy(C₂-C₅)alkyloxy and N-heterocyclacyl, C₁-C₃ alkylsulfonyl, sulfonamide and C₁-C₃ alkylsulfonamide;

and iv) a divalent group of the formula:



wherein each carbonyl of the divalent group bonds to the nitrogen to form a five membered ring and R_a is as defined above;

B is selected from -OH; C₁-C₆ alkyl or C₁-C₆ alkyl amino, di(C₁-C₆ alkyl)amino, C₁-C₆ alkyloxy, N-heterocyclic and



each n' is independently 0, 1 or 2;

m is 0, 1, 2 or 3;

and G is N or O;

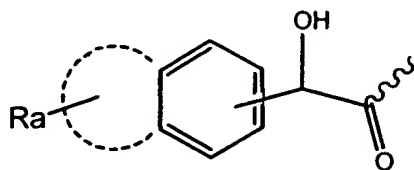
J is selected from the group consisting of aryl having a 5 to 6 membered ring optionally including up to 2 heteroatoms selected from the N, O, and S; fused aryl rings of 8 to 14 atoms optionally including up to 3 heteroatoms selected from N, O, and S, mono or fused ring cycloalkyl having 5 to 12 carbon atoms; and mono or fused ring heterocyclic having 5 to 12 carbon atoms including up to 3 heteroatoms chosen from the group consisting of N, O, and S;

each K is chosen from OH, C₁-C₃ alkyl; C₁-C₆ alkylacylamino, C₁-C₆ alkylacyloxy, C₁-C₆ alkyloxy, C₁-C₆ alkylthioxy, amido (including primary, C₁-C₆ alkyl and phenyl secondary and tertiary), NH₂, mono and di(C₁-C₆ alkyl and phenyl) amino, carbamyl (including C₁-C₆ alkyl and phenyl amides and esters), carboxyl (including C₁-C₆ alkyl and phenyl esters) and carboxy(C₂-C₅)alkyloxy;

R₁ is straight or branched chain C₁-C₅ alkanyl or C₂-C₅ alkenyl;

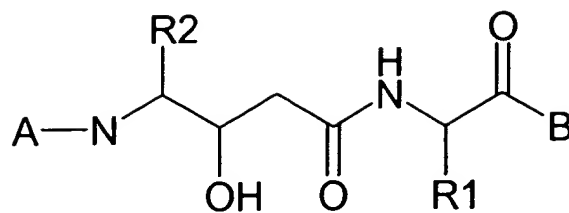
R₂ is C₁₋₅ straight or branched chain alkanyl or alkenyl; methylthiomethyl; aryl or arylalkyl or heteroaryl or heteroarylalkyl wherein any of the above are optionally substituted with up to 2 of C₁₋₃ alkyl, trifluoromethyl or halogen, and stereoisomers, hydrates or pharmaceutically acceptable salts thereof.

2) The compound claim 1 wherein A is:



wherein the dotted line indicates an optional aryl ring fused to the phenyl ring.

24) A method of slowing or ameliorating the progression of a disease state characterized by deposition of A β peptide in a mammal comprising administering to a mammal in need thereof an effective amount of a compound of formula 1

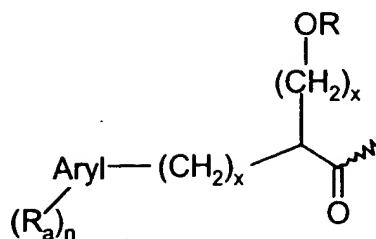


Formula 1

wherein:

A is

i)



wherein Aryl is mono or bicyclic and has from 5 to 10 ring atoms and may optionally include up to 3 heteroatoms chosen from N, O and S;

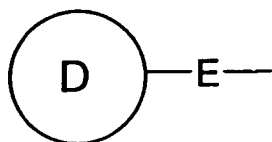
each x is independently 0, 1 or 2;

R is H, C₁-C₆ alkyl, phenyl or benzyl wherein each phenyl ring is optionally substituted with up to two groups independently selected from -OH; -CH₂OH, -CO₂H, -CF₃, Cl, Br, F; and C₁-C₂ alkyl;

each R_a is independently selected from the group consisting of H, OH, C₁-C₃ alkyl; C₁-C₆ alkylacylamino, C₁-C₆ alkylacyloxy, C₁-C₆ alkyloxy, C₁-C₆ alkylthioxy, amido (including primary, C₁-C₆ alkyl and phenyl secondary and tertiary), NH₂, mono and di(C₁-C₆ alkyl and phenyl) amino, carbamyl (including C₁-C₆ alkyl and phenyl amides and esters), carboxyl (including C₁-C₆ alkyl and phenyl esters), carboxy(C₂-C₅)alkyloxy and N-heterocyclacyl;

and n is 1 or 2;

ii)



wherein D is chosen from aryl having 5 to 6 atoms, optionally including up to 2 heteroatoms selected from the N, O, and S; fused aryl of 8 to 14 atoms optionally including up to

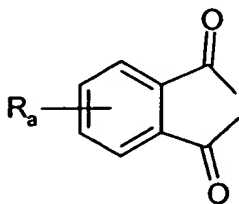
3 heteroatoms selected from the N, O, and S; mono or fused cycloalkyl having 5 to 12 carbon atoms; and mono or fused heterocycloalkyl having 5 to 12 carbon atoms including up to 3 heteroatoms selected from N, O, and S; biaryl, diaryl ether, diarylketone, and phenyl(C₁-C₈) alkyloxyaryl;

and wherein E is a divalent group chosen from carbonyl, sulfonyl, C₁-C₃ alkylene, -X- (C₁-C₃) alkylcarbonyl wherein X is chosen from N, O and S, or E is merely a bond;

and D may optionally be substituted with up to two groups chosen from OH, C₁-C₃ alkyl; C₁-C₆ alkylacylamino, C₁-C₆ alkylacyloxy, C₁-C₆ alkyloxy, C₁-C₆ alkylthioxy, amido (including primary, C₁-C₆ alkyl and phenyl secondary and tertiary), NH₂, mono and di(C₁-C₆ alkyl and phenyl) amino, carbamyl (including C₁-C₆ alkyl and phenyl amides and esters), carboxyl (including C₁-C₆ alkyl and phenyl esters), carboxy(C₂-C₅)alkyloxy, N-heterocyclylacyl, C₁-C₃ alkylsulfonyl, sulfonamide and C₁-C₃ alkylsulfonamide;

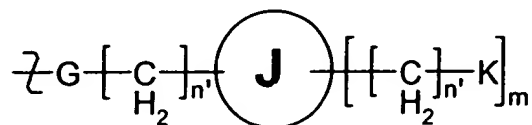
iii) C₁-C₆ alkanoyl; C₂-C₆ alkenoyl; and methylthioC₁-C₅ alkanoyl, any of which may be substituted with up to two groups chosen from OH, C₁-C₆ alkylacylamino, C₁-C₆ alkylacyloxy; C₁-C₆ alkyloxy; C₁-C₆ alkylthioxy, amido (including primary, C₁-C₆ alkyl and phenyl secondary and tertiary), amino, C₁-C₆ alkyl and phenyl amino, carbamyl (including C₁-C₆ alkyl and phenyl amides and esters), carboxyl (including C₁-C₆ alkyl and phenyl esters), carboxy(C₂-C₅)alkyloxy and N-heterocyclylacyl, C₁-C₃ alkylsulfonyl, sulfonamide and C₁-C₃ alkylsulfonamide;

and iv) a divalent group of the formula:



wherein each carbonyl of the divalent group bonds to the nitrogen to form a five membered ring and R_a is as defined above;

B is selected from -OH; C₁-C₆ alkyl or C₁-C₆ alkyl amino, di(C₁-C₆ alkyl)amino, C₁-C₆ alkyloxy, N-heterocyclic and



each n' is independently 0, 1 or 2;

m is 0, 1, 2 or 3;

and G is N or O;

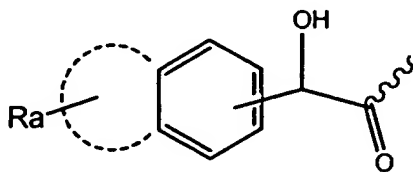
J is selected from the group consisting of aryl having a 5 to 6 membered ring optionally including up to 2 heteroatoms selected from the N, O, and S; fused aryl rings of 8 to 14 atoms optionally including up to 3 heteroatoms selected from N, O, and S, mono or fused ring cycloalkyl having 5 to 12 carbon atoms; and mono or fused ring heterocyclic having 5 to 12 carbon atoms including up to 3 heteroatoms chosen from the group consisting of N, O, and S;

each K is chosen from OH, C₁-C₃ alkyl; C₁-C₆ alkylacylamino, C₁-C₆ alkylacyloxy, C₁-C₆ alkyloxy, C₁-C₆ alkylthioxy, amido (including primary, C₁-C₆ alkyl and phenyl secondary and tertiary), NH₂, mono and di(C₁-C₆ alkyl and phenyl) amino, carbamyl (including C₁-C₆ alkyl and phenyl amides and esters), carboxyl (including C₁-C₆ alkyl and phenyl esters) and carboxy(C₂-C₅)alkyloxy;

R₁ is straight or branched chain C₁-C₅ alkanyl or C₂-C₅ alkenyl;

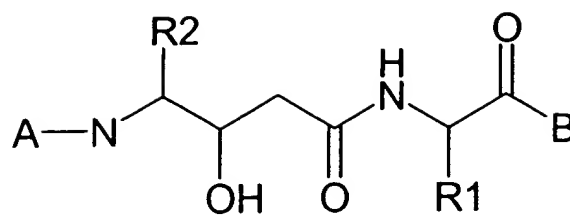
R₂ is C₁₋₅ straight or branched chain alkanyl or alkenyl; methylthiomethyl; aryl or arylalkyl or heteroaryl or heteroarylalkyl wherein any of the above are optionally substituted with up to 2 of C₁₋₃ alkyl, trifluoromethyl or halogen, and pharmaceutically acceptable salts and esters thereof.

25) The method claim 24 wherein A is:



wherein the dotted line indicates an optional aryl ring fused to the phenyl ring.

47) A pharmaceutical composition comprising a compound of formula 1

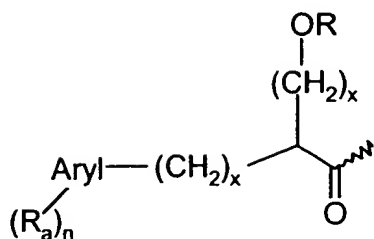


Formula 1

wherein:

A is

i)



wherein Aryl is mono or bicyclic and has from 5 to 10 ring atoms and may optionally include up to 3 heteroatoms chosen from N, O and S;

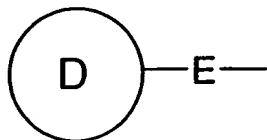
each x is independently 0, 1 or 2;

R is H, C₁-C₆ alkyl, phenyl or benzyl wherein each phenyl ring is optionally substituted with up to two groups independently selected from -OH; -CH₂OH, -CO₂H, -CF₃, Cl, Br, F; and C₁-C₂ alkyl;

each R_a is independently selected from the group consisting of H, OH, C₁-C₃ alkyl; C₁-C₆ alkylacylamino, C₁-C₆ alkylacyloxy, C₁-C₆ alkyloxy, C₁-C₆ alkylthioxy, amido (including primary, C₁-C₆ alkyl and phenyl secondary and tertiary), NH₂, mono and di(C₁-C₆ alkyl and phenyl) amino, carbamyl (including C₁-C₆ alkyl and phenyl amides and esters), carboxyl (including C₁-C₆ alkyl and phenyl esters), carboxy(C₂-C₃)alkyloxy and N-heterocyclacyl;

and n is 1 or 2;

ii)



wherein D is chosen from aryl having 5 to 6 atoms, optionally including up to 2 heteroatoms selected from the N, O, and S; fused aryl of 8 to 14 atoms optionally including up to

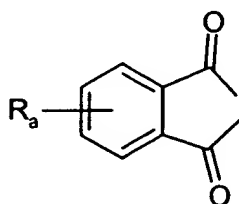
3 heteroatoms selected from the N, O, and S; mono or fused cycloalkyl having 5 to 12 carbon atoms; and mono or fused heterocycloalkyl having 5 to 12 carbon atoms including up to 3 heteroatoms selected from N, O, and S; biaryl, diaryl ether, diarylketone, and phenyl(C₁-C₈) alkyloxyaryl;

and wherein E is a divalent group chosen from carbonyl, sulfonyl, C₁-C₃ alkylene, -X- (C₁-C₃) alkylcarbonyl wherein X is chosen from N, O and S, or E is merely a bond;

and D may optionally be substituted with up to two groups chosen from OH, C₁-C₃ alkyl; C₁-C₆ alkylacylamino, C₁-C₆ alkylacyloxy, C₁-C₆ alkyloxy, C₁-C₆ alkylthioxy, amido (including primary, C₁-C₆ alkyl and phenyl secondary and tertiary), NH₂, mono and di(C₁-C₆ alkyl and phenyl) amino, carbamyl (including C₁-C₆ alkyl and phenyl amides and esters), carboxyl (including C₁-C₆ alkyl and phenyl esters), carboxy(C₂-C₅)alkyloxy, N-heterocyclacyl, C₁-C₃ alkylsulfonyl, sulfonamide and C₁-C₃ alkylsulfonamide;

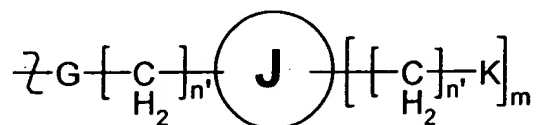
iii) C₁-C₆ alkanoyl; C₂-C₆ alkenoyl; and methylthioC₁-C₅ alkanoyl, any of which may be substituted with up to two groups chosen from OH, C₁-C₆ alkylacylamino, C₁-C₆ alkylacyloxy; C₁-C₆ alkyloxy; C₁-C₆ alkylthioxy, amido (including primary, C₁-C₆ alkyl and phenyl secondary and tertiary), amino, C₁-C₆ alkyl and phenyl amino, carbamyl (including C₁-C₆ alkyl and phenyl amides and esters), carboxyl (including C₁-C₆ alkyl and phenyl esters), carboxy(C₂-C₅)alkyloxy and N-heterocyclacyl, C₁-C₃ alkylsulfonyl, sulfonamide and C₁-C₃ alkylsulfonamide;

and iv) a divalent group of the formula:



wherein each carbonyl of the divalent group bonds to the nitrogen to form a five-membered ring and R_a is as defined above;

B is selected from -OH; C₁-C₆ alkyl or C₁-C₆ alkyl amino, di(C₁-C₆ alkyl)amino, C₁-C₆ alkyloxy, N-heterocyclic and



each n' is independently 0, 1 or 2;

m is 0, 1, 2 or 3;

and G is N or O;

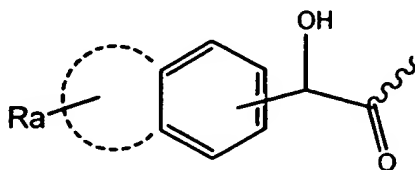
J is selected from the group consisting of aryl having a 5 to 6 membered ring optionally including up to 2 heteroatoms selected from the N, O, and S; fused aryl rings of 8 to 14 atoms optionally including up to 3 heteroatoms selected from N, O, and S, mono or fused ring cycloalkyl having 5 to 12 carbon atoms; and mono or fused ring heterocyclic having 5 to 12 carbon atoms including up to 3 heteroatoms chosen from the group consisting of N, O, and S;

each K is chosen from OH, C₁-C₃ alkyl; C₁-C₆ alkylacylamino, C₁-C₆ alkylacyloxy, C₁-C₆ alkyloxy, C₁-C₆ alkylthioxy, amido (including primary, C₁-C₆ alkyl and phenyl secondary and tertiary), NH₂, mono and di(C₁-C₆ alkyl and phenyl) amino, carbamyl (including C₁-C₆ alkyl and phenyl amides and esters), carboxyl (including C₁-C₆ alkyl and phenyl esters) and carboxy(C₂-C₅)alkyloxy;

R₁ is straight or branched chain C₁-C₅ alkanyl or C₂-C₅ alkenyl;

R₂ is C₁₋₅ straight or branched chain alkanyl or alkenyl; methylthiomethyl; aryl or arylalkyl or heteroaryl or heteroarylalkyl wherein any of the above are optionally substituted with up to 2 of C₁₋₃ alkyl, trifluoromethyl or halogen, and pharmaceutically acceptable salts and esters thereof and a pharmaceutically acceptable diluent.

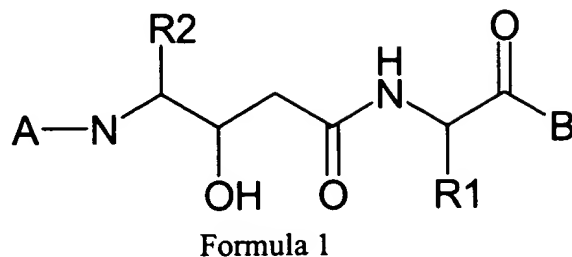
48) The composition claim 47 wherein A is:



wherein the dotted line indicates an optional aryl ring fused to the phenyl ring.

Marked up copy of claim amendments:

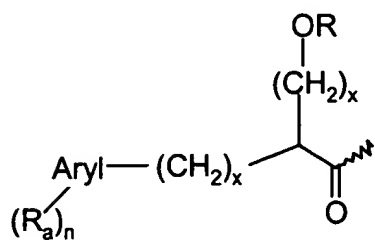
1) A compound of formula 1



wherein:

A is

i)



wherein Aryl is mono or bicyclic and has from 5 to 10 ring atoms and may optionally include up to 3 heteroatoms chosen from N, O and S;

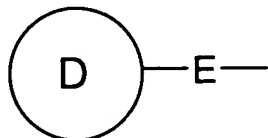
each x is independently 0, 1 or 2;

R is H, C₁-C₆ alkyl, phenyl or benzyl wherein each phenyl ring is optionally substituted with up to two groups independently selected from -OH; -CH₂OH, -CO₂H, -CF₃, Cl, Br, F; and C₁-C₂ alkyl;

each R_a is independently selected from the group consisting of H, OH, C₁-C₃ alkyl; C₁-C₆ alkylacylamino, C₁-C₆ alkylacyloxy, C₁-C₆ alkyloxy, C₁-C₆ alkylthioxy, amido (including primary, C₁-C₆ alkyl and phenyl secondary and tertiary), NH₂, mono and di(C₁-C₆ alkyl and phenyl) amino, carbamyl (including C₁-C₆ alkyl and phenyl amides and esters), carboxyl (including C₁-C₆ alkyl and phenyl esters), carboxy(C₂-C₅)alkyloxy and N-heterocyclacyl;

and n is 1 or 2;

ii)



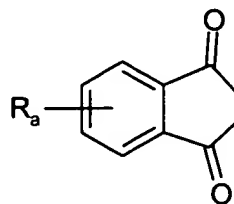
wherein D is chosen from aryl having 5 to 6 atoms, optionally including up to 2 heteroatoms selected from the N, O, and S; fused aryl of 8 to 14 atoms optionally including up to 3 heteroatoms selected from the N, O, and S; mono or fused cycloalkyl having 5 to 12 carbon atoms; and mono or fused heterocycloalkyl having 5 to 12 carbon atoms including up to 3 heteroatoms selected from N, O, and S; biaryl, diaryl ether, diarylketone, and phenyl(C₁-C₈) alkyloxyaryl;

and wherein E is a divalent group chosen from carbonyl, sulfonyl, C₁-C₃ alkylene, -X- (C₁-C₃) alkylcarbonyl wherein X is chosen from N, O and S, or E is merely a bond;

and D may optionally be substituted with up to two groups chosen from OH, C₁-C₃ alkyl; C₁-C₆ alkylacylamino, C₁-C₆ alkylacyloxy, C₁-C₆ alkyloxy, C₁-C₆ alkylthioxy, amido (including primary, C₁-C₆ alkyl and phenyl secondary and tertiary), NH₂, mono and di(C₁-C₆ alkyl and phenyl) amino, carbamyl (including C₁-C₆ alkyl and phenyl amides and esters), carboxyl (including C₁-C₆ alkyl and phenyl esters), carboxy(C₂-C₅)alkyloxy, N-heterocyclylacyl, C₁-C₃ alkylsulfonyl, sulfonamide and C₁-C₃ alkylsulfonamide;

iii) C₁-C₆ alkanoyl; C₂-C₆ alkenoyl; and methylthioC₁-C₅ alkanoyl, any of which may be substituted with up to two groups chosen from OH, C₁-C₆ alkylacylamino, C₁-C₆ alkylacyloxy; C₁-C₆ alkyloxy; C₁-C₆ alkylthioxy : amido [(including primary, C₁-C₆ alkyl secondary; C₁-C₆ alkyl and phenyl tertiary, amino] (including primary, C₁-C₆ alkyl and phenyl secondary and tertiary), amino, C₁-C₆ alkyl and phenyl amino, carbamyl (including C₁-C₆ alkyl and phenyl amides and esters), carboxyl (including C₁-C₆ alkyl and phenyl esters), carboxy(C₂-C₅)alkyloxy and N-heterocyclylacyl, C₁-C₃ alkylsulfonyl, sulfonamide and C₁-C₃ alkylsulfonamide;

and iv) a divalent group of the formula:



wherein each carbonyl of the divalent group bonds to the nitrogen to form a five membered ring and R_a is as defined above;

B is selected from -OH; C₁-C₆ alkyl or C₁-C₆ alkyl amino, di(C₁-C₆ alkyl)amino, C₁-C₆ alkyloxy, N-heterocyclylic and



NO

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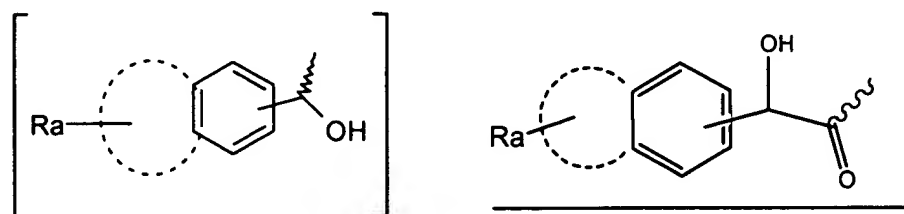
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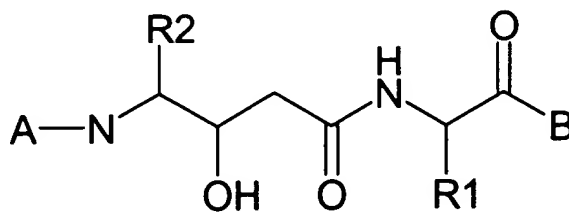
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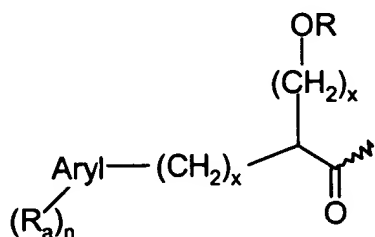


Formula 1

wherein:

A is

i)



wherein Aryl is mono or bicyclic and has from 5 to 10 ring atoms and may optionally include up to 3 heteroatoms chosen from N, O and S;

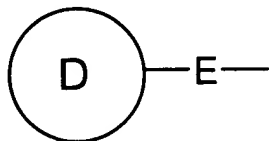
each x is independently 0, 1 or 2;

R is H, C₁-C₆ alkyl, phenyl or benzyl wherein each phenyl ring is optionally substituted with up to two groups independently selected from -OH; -CH₂OH, -CO₂H, -CF₃, Cl, Br, F; and C₁-C₂ alkyl;

each R_a is independently selected from the group consisting of H, OH, C₁-C₃ alkyl; C₁-C₆ alkylacylamino, C₁-C₆ alkylacyloxy, C₁-C₆ alkyloxy, C₁-C₆ alkylthioxy, amido (including primary, C₁-C₆ alkyl and phenyl secondary and tertiary), NH₂, mono and di(C₁-C₆ alkyl and phenyl) amino, carbamyl (including C₁-C₆ alkyl and phenyl amides and esters), carboxyl (including C₁-C₆ alkyl and phenyl esters), carboxy(C₂-C₅)alkyloxy and N-heterocyclacyl;

and n is 1 or 2;

ii)



wherein D is chosen from aryl having 5 to 6 atoms, optionally including up to 2 heteroatoms selected from the N, O, and S; fused aryl of 8 to 14 atoms optionally including up to

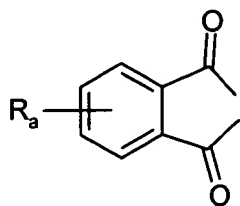
3 heteroatoms selected from the N, O, and S; mono or fused cycloalkyl having 5 to 12 carbon atoms; and mono or fused heterocycloalkyl having 5 to 12 carbon atoms including up to 3 heteroatoms selected from N, O, and S; biaryl, diaryl ether; diarylketone, and phenyl(C₁-C₈) alkyloxyaryl;

and wherein E is a divalent group chosen from carbonyl, sulfonyl, C₁-C₃ alkylene, -X- (C₁-C₃) alkylcarbonyl wherein X is chosen from N, O and S, or E is merely a bond;

and D may optionally be substituted with up to two groups chosen from OH, C₁-C₃ alkyl; C₁-C₆ alkylacylamino, C₁-C₆ alkylacyloxy, C₁-C₆ alkyloxy, C₁-C₆ alkylthioxy, amido (including primary, C₁-C₆ alkyl and phenyl secondary and tertiary), NH₂, mono and di(C₁-C₆ alkyl and phenyl) amino, carbamyl (including C₁-C₆ alkyl and phenyl amides and esters), carboxyl (including C₁-C₆ alkyl and phenyl esters), carboxy(C₂-C₅)alkyloxy, N-heterocyclacyl, C₁-C₃ alkylsulfonyl, sulfonamide and C₁-C₃ alkylsulfonamide;

iii) C₁-C₆ alkanoyl; C₂-C₆ alkenoyl; and methylthioC₁-C₅ alkanoyl, any of which may be substituted with up to two groups chosen from OH, C₁-C₆ alkylacylamino, C₁-C₆ alkylacyloxy; C₁-C₆ alkyloxy; C₁-C₆ alkylthioxy, amido [(including primary, C₁-C₆ alkyl secondary; C₁-C₆ alkyl and phenyl tertiary)] (including primary, C₁-C₆ alkyl and phenyl secondary and tertiary), amino, C₁-C₆ alkyl and phenyl amino, carbamyl (including C₁-C₆ alkyl and phenyl amides and esters), carboxyl (including C₁-C₆ alkyl and phenyl esters), carboxy(C₂-C₅)alkyloxy and N-heterocyclacyl, C₁-C₃ alkylsulfonyl, sulfonamide and C₁-C₃ alkylsulfonamide;

and iv) a divalent group of the formula:



wherein each carbonyl of the divalent group bonds to the nitrogen to form a five membered ring and Ra is as defined above;

B is selected from -OH; C₁-C₆ alkyl or C₁-C₆ alkyl amino, di(C₁-C₆ alkyl)amino, C₁-C₆ alkyloxy, N-heterocyclic and



each n' is independently 0, 1 or 2;

m is 0, 1, 2 or 3;

and G is N or O;

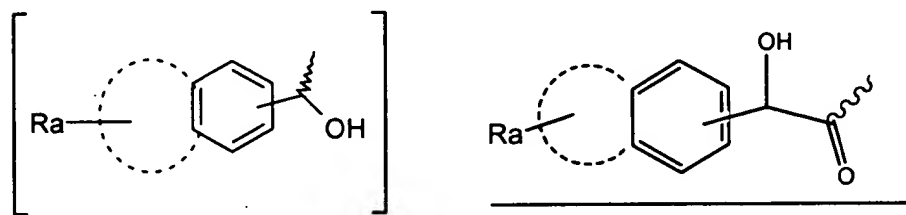
J is selected from the group consisting of aryl having a 5 to 6 membered ring optionally including up to 2 heteroatoms selected from the N, O, and S; fused aryl rings of 8 to 14 atoms optionally including up to 3 heteroatoms selected from N, O, and S, mono or fused ring cycloalkyl having 5 to 12 carbon atoms; and mono or fused ring heterocyclic having 5 to 12 carbon atoms including up to 3 heteroatoms chosen from the group consisting of N, O, and S;

each K is chosen from OH, C₁-C₃ alkyl; C₁-C₆ alkylacylamino, C₁-C₆ alkylacyloxy, C₁-C₆ alkyloxy, C₁-C₆ alkylthioxy, amido (including primary, C₁-C₆ alkyl and phenyl secondary and tertiary), NH₂, mono and di(C₁-C₆ alkyl and phenyl) amino, carbamyl (including C₁-C₆ alkyl and phenyl amides and esters), carboxyl (including C₁-C₆ alkyl and phenyl esters) and carboxy(C₂-C₅)alkyloxy;

R₁ is straight or branched chain C₁-C₅ alkanyl or C₂-C₅ alkenyl;

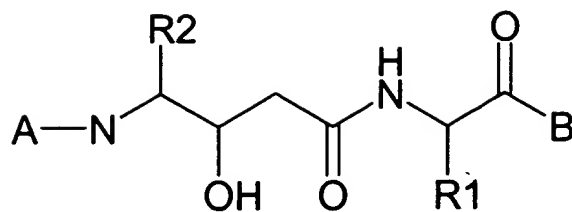
R₂ is C₁₋₅ straight or branched chain alkanyl or alkenyl; methylthiomethyl; aryl or arylalkyl or heteroaryl or heteroarylalkyl wherein any of the above are optionally substituted with up to 2 of C₁₋₃ alkyl, trifluoromethyl or halogen, and pharmaceutically acceptable salts and esters thereof.

25) The method claim 24 wherein A is:



wherein the dotted line indicates an optional aryl ring fused to the phenyl ring.

47) A pharmaceutical composition comprising a compound of formula 1

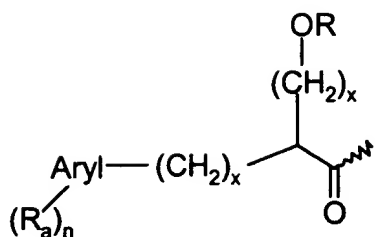


Formula 1

wherein:

A is

i)



wherein Aryl is mono or bicyclic and has from 5 to 10 ring atoms and may optionally include up to 3 heteroatoms chosen from N, O and S;

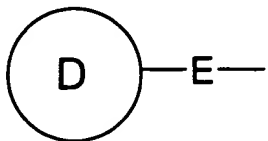
each x is independently 0, 1 or 2;

R is H, C₁-C₆ alkyl, phenyl or benzyl wherein each phenyl ring is optionally substituted with up to two groups independently selected from -OH; -CH₂OH, -CO₂H, -CF₃, Cl, Br, F; and C₁-C₂ alkyl;

each R_a is independently selected from the group consisting of H, OH, C₁-C₃ alkyl; C₁-C₆ alkylacylamino, C₁-C₆ alkylacyloxy, C₁-C₆ alkyloxy, C₁-C₆ alkylthioxy, amido (including primary, C₁-C₆ alkyl and phenyl secondary and tertiary), NH₂, mono and di(C₁-C₆ alkyl and phenyl) amino, carbamyl (including C₁-C₆ alkyl and phenyl amides and esters), carboxyl (including C₁-C₆ alkyl and phenyl esters), carboxy(C₂-C₅)alkyloxy and N-heterocyclacyl;

and n is 1 or 2;

ii)



wherein D is chosen from aryl having 5 to 6 atoms, optionally including up to 2 heteroatoms selected from the N, O, and S; fused aryl of 8 to 14 atoms optionally including up to

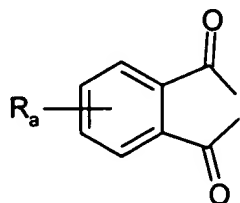
3 heteroatoms selected from the N, O, and S; mono or fused cycloalkyl having 5 to 12 carbon atoms; and mono or fused heterocycloalkyl having 5 to 12 carbon atoms including up to 3 heteroatoms selected from N, O, and S; biaryl, diaryl ether; diarylketone, and phenyl(C₁-C₈) alkyloxyaryl;

and wherein E is a divalent group chosen from carbonyl, sulfonyl, C₁-C₃ alkylene, -X- (C₁-C₃) alkylcarbonyl wherein X is chosen from N, O and S, or E is merely a bond;

and D may optionally be substituted with up to two groups chosen from OH, C₁-C₃ alkyl; C₁-C₆ alkylacylamino, C₁-C₆ alkylacyloxy, C₁-C₆ alkyloxy, C₁-C₆ alkylthioxy, amido (including primary, C₁-C₆ alkyl and phenyl secondary and tertiary), NH₂, mono and di(C₁-C₆ alkyl and phenyl) amino, carbamyl (including C₁-C₆ alkyl and phenyl amides and esters), carboxyl (including C₁-C₆ alkyl and phenyl esters), carboxy(C₂-C₅)alkyloxy, N-heterocyclylacyl, C₁-C₃ alkylsulfonyl, sulfonamide and C₁-C₃ alkylsulfonamide;

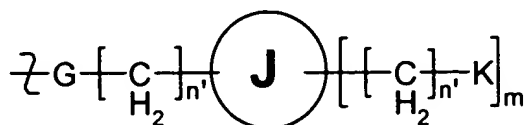
iii) C₁-C₆ alkanoyl; C₂-C₆ alkenoyl; and methylthioC₁-C₅ alkanoyl, any of which may be substituted with up to two groups chosen from OH, C₁-C₆ alkylacylamino, C₁-C₆ alkylacyloxy; C₁-C₆ alkyloxy; C₁-C₆ alkylthioxy, amido amido [(including primary, C₁-C₆ alkyl secondary; C₁-C₆ alkyl and phenyl tertiary, amino] (including primary, C₁-C₆ alkyl and phenyl secondary and tertiary), amino, C₁-C₆ alkyl and phenyl amino, carbamyl (including C₁-C₆ alkyl and phenyl amides and esters), carboxyl (including C₁-C₆ alkyl and phenyl esters), carboxy(C₂-C₅)alkyloxy and N-heterocyclylacyl, C₁-C₃ alkylsulfonyl, sulfonamide and C₁-C₃ alkylsulfonamide;

and iv) a divalent group of the formula:



wherein each carbonyl of the divalent group bonds to the nitrogen to form a five-membered ring and R_a is as defined above;

B is selected from -OH; C₁-C₆ alkyl or C₁-C₆ alkyl amino, di(C₁-C₆ alkyl)amino, C₁-C₆ alkyloxy, N-heterocyclylic and



each n' is independently 0, 1 or 2;

m is 0, 1, 2 or 3;

and G is N or O;

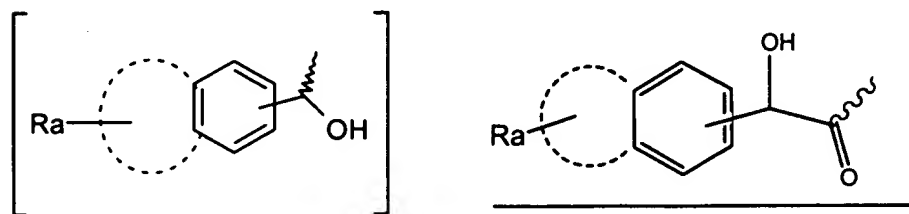
J is selected from the group consisting of aryl having a 5 to 6 membered ring optionally including up to 2 heteroatoms selected from the N, O, and S; fused aryl rings of 8 to 14 atoms optionally including up to 3 heteroatoms selected from N, O, and S, mono or fused ring cycloalkyl having 5 to 12 carbon atoms; and mono or fused ring heterocyclic having 5 to 12 carbon atoms including up to 3 heteroatoms chosen from the group consisting of N, O, and S;

each K is chosen from OH, C₁-C₃ alkyl; C₁-C₆ alkylacylamino, C₁-C₆ alkylacyloxy, C₁-C₆ alkyloxy, C₁-C₆ alkylthioxy, amido (including primary, C₁-C₆ alkyl and phenyl secondary and tertiary), NH₂, mono and di(C₁-C₆ alkyl and phenyl) amino, carbamyl (including C₁-C₆ alkyl and phenyl amides and esters), carboxyl (including C₁-C₆ alkyl and phenyl esters) and carboxy(C₂-C₅)alkyloxy;

R₁ is straight or branched chain C₁-C₅ alkanyl or C₂-C₅ alkenyl;

R₂ is C₁₋₅ straight or branched chain alkanyl or alkenyl; methylthiomethyl; aryl or arylalkyl or heteroaryl or heteroarylalkyl wherein any of the above are optionally substituted with up to 2 of C₁₋₃ alkyl, trifluoromethyl or halogen, and pharmaceutically acceptable salts and esters thereof and a pharmaceutically acceptable diluent.

48) The composition claim 47 wherein A is:



wherein the dotted line indicates an optional aryl ring fused to the phenyl ring.